REMARKS

Applicants have amended claims 13 and 168 and added new claims 173-196. Basis for the amendments and new claims is found in the specification and originally filed claims, particularly claims 159, 161, 162, 171, and 172. Applicants have also cancelled, without prejudice, claim 159.

35 U.S.C. §103

Claims 13-18, 20, 23-32, 118, 128-130, 132, 135-144, 156-158, and 168 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Higuchi et al. in view of Haff et al. Specifically the Examiner believes it would have been obvious to use real-time fluorescent monitoring taught in the Higuchi reference with the faster heating rate as described in the Haff reference, as the Haff reference teaches that the instrument of the Higuchi reference is comparable to the instrument of the Haff reference. Applicants respectfully traverse and request reconsideration.

The rejected claims are directed to a system for performing PCR and monitoring the reaction during the cycling. The system of the rejected claims comprises a means for both heating and cooling the sample at a rate of at least 0.5°C and a means for monitoring the fluorescence of the sample during the heating and cooling cycles. The means for monitoring fluorescence illustratively comprises a light emitting source and a light detector positioned to illuminate the sample and measure the fluorescence respectively. Applicants submit that neither the Higuchi reference or the Haff reference, either alone or together, teaches or suggests the system of the present invention. First, while the Haff reference arguably teaches heating the sample at a rate of 0.77°C/sec, neither reference teaches the rapid *cooling* of the sample. Second, neither the Higuchi reference nor the Haff reference teach or suggest a means for positioning a sample container in a monitoring position. The Haff reference teaches that the samples are encased in a metal block. Likewise, the Higuchi reference does not teach a means for positioning the sample. In both references, the samples are merely placed in a sample holder.

Furthermore, upon reading the Higuchi and Haff references, the skilled artisan would not be motivated to use the system of the Haff reference with the fluorescent monitoring of the Higuchi reference. The Haff reference describes a method for PCR using a PE9600 instrument in which rapid heating is obtained by encasing sample tubes in recesses in a metal heating block such that the heating block is in close contact with the sample tube.

The Haff reference teaches that it is necessary to encase the sample tube in the metal block to obtain the rapid heating. As the sample vessel holder in the Haff reference is not an optically clear material, the only way to monitor the sample by fluorescence during the heating and cooling cycles would be to have an individual probe inserted into each tube, as taught by the Higuchi reference. However, in Haff, temperature probes were inserted into the samples to compare the temperature of the metal block to the temperature of the sample, and the presence of the probes were found to disturb the sample temperature. For this reason, the Haff reference teaches that it is undesirable to have a probe in the sample. See Haff, page 107, first column, second full paragraph. Thus, a person of ordinary skill in the art would not use the faster PE9600 with the probe system as taught by Higuchi.

Additionally, in an effort to expedite prosecution of this case, but in no way conceding to the validity of the rejection, Applicants have amended claims 13 and 168 to recite a means for heating and a means for cooling a sample of at least 1.0°C/sec. This rate of heating and cooling is not taught or suggested by either the Higuchi reference nor the Haff reference, which arguably teaches a heating rate of 0.77°C/sec.

Applicants thus submit that the combination of the teachings of the Higuchi and Haff reference, either alone or together, would not lead the skilled artisan to the system having a means for positioning a sample container in a monitoring position as well as having a means for heating and cooling the sample at a rate of about 1.0°C/sec. Applicants therefore request withdrawal of the rejection.

Claims 13-20, 23-25, 28-31, 128-132, 135-137, 140-143, 156-160, and 168-170 have been rejected under 35 U.S.C. §103(a) as being unpatenable over U.S. Patent No. 5,720,923 (the '923 patent) issued to Haff et al. Applicants respectfully traverse and request reconsideration.

When determining obviousness both the claimed invention and the reference must be taken as whole and the reference must suggest the desirability of combining elements or changing elements to provide the claimed invention. Furthermore, the references must be viewed without hindsight. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143, n.5, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). The Examiner is not allowed to use the claims or the specification as a blueprint to combine elements if there is no suggestion or motivation to do so. Applicants submit that the '923 patent, *taken as a whole*, does not teach or suggest the present invention. The '923 patent describes a number of different systems that may be used for PCR. However, the '923 patent does not teach that the individual elements or aspects of each system is interchangeable with the other. The Examiner has improperly used the present

invention as a blueprint to choose those unrelated elements from the '923 patent to support an obviousness rejection.

The '923 patent teaches an embodiment having a rotating cylindrical drum that includes a heat exchanger assembly. Flexible capillary tubes containing the sample remain fixed in place under the drum and are in contact with the drum. The drum then rotates, thereby exposing the stationary sample to different temperature zones. The '923 patent also teaches that the apparatus can have a fluorescent monitoring system to monitor the annealing and denaturation of the sample in real time. The '923 patent does not teach that this embodiment has a control means for rapidly heating and cooling the sample at a rate of at least 1.0°C/sec. There is also no teaching or suggestion that the heating means used for the other apparatus described in the '923 patent can be used with this specific embodiment in place of the heat exchange drum.

The '923 patent teaches an alternative embodiment that can cycle between annealing and denaturation in as little as 8 seconds. From this information, the Examiner has calculated that the rate of temperature change during the cycling would be 8.75°C/sec. The Examiner appears to have grafted this rate onto the embodiment having rotary drum and there is simply no teaching that the rotary drum embodiment can employ such a heating and cooling rate. With this alternative embodiment, the sample is contained in a thin wall capillary tube held stationary inside a chamber and hot and cold water are alternately pumped in and out of the chamber. This alternative embodiment however, contains no means to position the sample in a monitoring position, nor is there any suggestion of how to do so. Furthermore, the '923 patent teaches that the capillary tubing for holding the sample in this embodiment is preferably metal or plastic, with the plastic being Teflon or polypropylene. The nature of the capillary material is essential for the rapid heating and cooling with the exchanging water baths. These materials, however, are not optically active. Thus, there is simply no teaching or suggestion that this alternative embodiment may be used for real-time monitoring. Therefore, the skilled artisan simply would not be able to combine the speed of this apparatus with the fluorescence monitoring system of the first apparatus described in the paragraph above.

Finally, none of the embodiments taught in the '923 patent have a means for positioning the sample container in a monitoring position. In each embodiment, the sample containers described all remain stationary. Contrary to the Examiner's contention, the drum of the first embodiment of the '923 patent moves the various temperature zones of a rotary heat exchanger. The rotating drum is not a carousel that holds and moves sample containers.

There is simply no suggestion in the '923 patent for moving the sample containers to a monitoring position.

Applicants therefore submit that the '923 patent, when taken as a whole, does not suggest or teach the present invention and respectfully request withdrawal of the rejection.

Claims 13-25, 28-31, 33-35, 55-59, 128-137, 140-143, 145, 146, 156-160, and 163-170 have been rejected under 35 U.S.C. §103(a) as being unpatentable over the '923 patent in view of U.S. Patent No. 4,326,342 issued to Schregenberger. Applicants respectfully traverse and request reconsideration.

Applicants submit that is would not have been obvious to combine the apparatus of the '923 patent with the oven of the Schregenberger reference to produce the claimed invention. As argued above, the '923 patent does not teach or suggest a system having a means for positioning the sample container in a monitoring position nor means for rapidly cooling and heating the sample at a rate of at least 1.0°C/second. The Schregenberger reference does not overcome these deficiencies. The Schregenberger reference teaches a multizone oven in which hot and cold air can be mixed together to provide a desired constant temperature. The hot air is kept at a desired pressure and the cold air at a desired flow rate to give the optimal mix to provide the desired temperature. However, the Schregenberger reference does not teach or suggest that the oven has a means for rapidly changing the temperature to cycle between hot and cold.

Applicants thus submit that the '923 patent and the Schregenberger reference, either alone or together do not teach the claimed system of the present invention. Applicants thus request withdrawal of the rejection.

Claims 13-35, 55-59, 79-82, 87-90, 118-125, 128-148, 151-160 and 163-170 have also been rejected under 35 U.S.C. §103(a) as being unpatentable over the '923 patent in view of the Schregenberger reference and in further view of U.S. Patent 4,325,910 issued to Jordon. Applicants respectfully traverse and request reconsideration.

As argued above, neither the '923 patent nor the Schregenberger reference, either alone or together, teach or suggest the present invention. The Jordon reference describes an automated multiple-purpose chemical analysis apparatus having a rotary carousel device in which samples are pipetted and mixed and then monitored by fluorescence. The apparatus is an analytical instrument for measuring components of serum samples and there is no motivation or teaching for the skilled artisan to use the carousel of the Jordon reference in a system for PCR. There certainly is no suggestion of how the teachings of the

Jordon reference can be combined with any of the specific embodiments of the '923 patent. Therefore, the Jordon reference does not overcome the deficiencies of the '923 patent or the Schregenberger reference and Applicants request withdrawal of the rejection.

Claims 13-35, 55-59, 79-82, 87-92, 118-160, and 163-170 have also been rejected under 35 U.S.C. §103(a) as being unpatentable over the '923 patent in view of the Schregenberger reference and the Jordon reference and in further view of U.S. Patent No. 5,472,603 issued to Schembri. Applicants respectfully traverse and request reconsideration.

As argued above, neither the '923 patent, the Schregenberger reference nor the Jordon reference, either alone or together, teach or suggest the present invention. The Schembri reference teaches an analytical rotor with a dye mixing chamber. The rotor is used for mixing reagents and then moving them into a capillary with increasing rotor speed. Again, there is no motivation nor would it have been obvious for the skilled artisan to use an analytical rotor used for mixing dyes in a system for doing PCR. It can further be argued that the skilled artisan would not be motivated to look at apparatus used in a different field, such as inorganic dyes, for use with a biological application such as PCR.

Applicants thus submit that the Schembri reference does not overcome the deficiencies of the '923 patent, the Schregenberger reference and/or the Jordon reference. None of the cited patents, either alone or together, teach or suggest the present invention. Applicants therefore request withdrawal of the rejection.

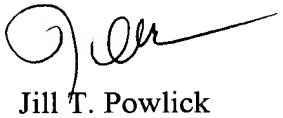
CLAIM OBJECTION

Claims 161, 162, 171, and 172 have been objected to as being dependent on rejected claims. These claims have been rewritten in independent form including all the limitations of the rejected independent claim and all intervening claims as new claims 173-214.

CONCLUSION

Applicants submit that the claims now stand ready for allowance and such allowance is courteously solicited. Should the Examiner have any questions or which to discuss this matter further, the Examiner is invited to call the Attorney below at (317) 231-7504.

Respectfully submitted



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Appendix to Amendment
Marked-Up Version
Application No. 08/869,275

IN THE TITLE:

Please amend the title as follows:

SYSTEM [AND METHOD] FOR MONITORING PCR PROCESS

IN THE CLAIMS:

Please amend claims 13 and 168 as follows:

13. (Four Times Amended) system for performing PCR and monitoring the reaction during temperature cycling comprising;

a sample container for holding a PCR sample, the sample container comprising an optically clear material, the sample container formed for holding less than 1 milliliter of a sample and having a first side, a second side, and an end;

means for positioning the PCR sample container in a monitoring position;

means for heating the PCR sample at a rate of at least [0.5°C/second] 1.0°C/second;

means for cooling the PCR sample at a rate of at least [0.5°C/second] 1.0°C/second;

control means for repeatedly operating the means for heating and the means for cooling to subject the PCR sample to thermal cycling;

means for optically exciting the sample to cause the sample to fluoresce; and

means for detecting the fluorescence of the excited sample during amplification when the sample is in the monitoring position.

168. (Amended) A system for carrying out and monitoring the progress of first and second biological reactions comprising:

first holding means for holding a first biological sample;

second holding means for holding a second biological sample;

transporting means for moving the first and second holding means between a non-monitoring position and a monitoring position;

thermal cycling means for repeatedly heating and cooling the first holding means and the second holding means in both the non-monitoring position and in the

monitoring position to carry out thermal cycling on both the first biological sample and the second biological sample, wherein the thermal cycling means heats and cools the first holding means and the second holding means at a rate of at least [0.5°C/second] 1.0°C/second;

monitoring means for ascertaining the progress of the first biological reaction in the first means for holding and the second biological reaction in the second means for holding when the first and second biological samples are in the monitoring position, the means for monitoring comprising means for detecting radiation emitted from the first and second biological samples; and

controlling means for controlling the operation of the transporting means, thermal cycling means, and the monitoring means such that the progress of the first and second biological reactions is detected as thermal cycling occurs.